

### **REMARKS**

Claims 12-26 are now currently pending in the present application. Claim 12 has been amended to recite the results obtained from performing the claimed method steps. Claim 15 has been amended to remove the exemplary language recited therein. Consequently, new claims 23 and 24 have been added to recite species of the groups recited in claim 15. Claim 18 has been amended in accordance with the specification, at least, at Example 8. New claims 25 and 26 have been added, which find support in the specification, at least, at page 8, lines 9-17; and page 9, lines 3-4. No new matter has been added by way of the present claim amendments.

The specification has been amended in the present response at page 9, lines 1-4. The amendment is due to an inadvertent clerical error, which is obvious in light of the preferred ratio disclosed thereafter. The specification has also been amended in the present response at page 16, lines 12-17. The amendment is due to an inadvertent clerical error, which is obvious in light of the title of the present invention and the descriptions in Examples 8 and 9. No new matter has been added by way of the present amendment of the specification.

### ***Objection to the Disclosure/Claim Objections***

The Examiner has objected to the specification and claim 18 because the range of 0.1:1 to 1:10, which is disclosed in the specification at page 3 and 9, and is recited in claim 18, is improper. Specifically, the claimed ratios are identical.

In response to the outstanding objections, Applicants have amended claim 18 and the present specification to recite that the ratio is 1:1 to 1:10. This corrects an inadvertent typographical error made in the present application. Moreover, it is clear that the amended ratio embraces the preferred ratio of 1:4 described in the specification at page 9, lines 1-4 and is consistent with Example 8 of the specification.

Applicants respectfully submit that an amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. *In re Odd*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971). See MPEP § 2163.07. Accordingly, Applicants respectfully request withdrawal of the outstanding objections.

***Objection to the Drawings***

The Examiner has objected to the drawings stating that the contents of Figures 2, 3A, 3B, 6, 8A and 9B are invisible. Applicants' representative placed a call to the Examiner to determine whether the Examiner reviewed the color drawings which were submitted with the **Petition to Accept Color Drawings and/or Photographs filed on June 22, 2006**. Applicants do not have any record of the USPTO's consideration of the previously-filed petition. However, Applicants direct the Examiner's attention to the USPTO Image File Wrapper entries of June 21, 2006 and June 22, 2006, which show the previously-filed Petition and payment of the requisite fee.

Accordingly, Applicants respectfully request consideration of the previously filed Petition. Moreover, on February 26, 2009, Applicants' representative discussed resubmitting the color drawings with the Examiner and advised the Examiner to contact the undersigned if the drawings can be viewed. Applicants respectfully request withdrawal of the outstanding objection to the drawings.

***Rejection under 35 U.S.C. §112, second paragraph – Indefiniteness***

Claim 15 stands rejected for reciting exemplary language in the claim (i.e., "such as").

In response to the outstanding rejection, Applicants have amended claim 15 to delete the exemplary language. Moreover, Applicants have added new claims 23 and 24, directed to the species recited in the exemplary clauses. Applicants respectfully request withdrawal of the outstanding rejection.

***Rejection under 35 U.S.C. §103 – Obviousness***

Claims 12-19 stand rejected under 35 U.S.C. § 103 as being unpatentable over US Patent Publication 2002/0142457 to Umezawa et al. (hereinafter "Umezawa") in view of Ranagappa and in further view of Egger, Bonnet, Gilmore and Lee.<sup>1</sup>

Applicants respectfully traverse.

The present invention possesses the following advantages:

- (i) the myocardial precursor cells and myocardial cells obtained from the method of the present invention are safe and avoid the possibility of malignant alteration because the cells are produced without genetic engineering; and
- (ii) the present invention enables differentiation of bone marrow cells into myocardial cells by a simple method in a shorter period of time (i.e., about three days) in contrast to the known method described by Umezawa, which requires complicated processes such as homogenization and demethylation, and a longer period of time.

The Examiner alleges that it would have been obvious for a person skilled in the art at the time the invention was made to combine the bone-marrow or cord-blood derived multipotential stem cells of Umezawa with the adipose-derived stroma stem cells of Rangappa in the method of myocardial differentiation of the mesenchymal stem cells (MSCs). The Examiner rationalized that this is because the method of differentiating bone-marrow or cord-blood derived mesenchymal stem cells into the cardiomyocytes of Umezawa is identical to the method of differentiating adipose-derived stromal MSCs of Rangappa (i.e., addition of 5-azacytidine). Thus, the present invention is obvious because it is equivalent to "duplicating components with similar functions within a composition". The Examiner further alleges that addition of 5-azacytidine is not "genetic engineering" which is precluded by the present claims, but rather is considered "epigenetic modification".

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<sup>1</sup> Please see the complete recitation of the rejection statement in the Office Action at page 5, the second paragraph.

Applicants respectfully disagree.

An important characteristic of the present invention is to induce the differentiation of bone marrow cells into myocardial cells or cord blood derived cells into a myocardial lineage by culturing with cells isolated from mammalian fat tissues or a culture supernatant thereof. The data disclosed in the specification clearly shows that any humoral factor(s) from cells isolated from fat tissues can affect the destiny of undifferentiated cells to lead them into a myocardial lineage. In the present invention, importantly, the differentiation of cells of interest into myocardial cells and/or precursor cells thereof does not require addition of 5-azacytidine to the culture system.

As mentioned above, the Examiner states that addition of 5-azacytidine is not considered to be "genetic engineering". However, 5-azacytidine is recognized to inhibit DNA methylation (Egger et al.). Inhibition of DNA methylation is a treatment for genetic material and alteration in DNA methylation necessarily changes gene expressions in cells. Thus, addition of 5-azacytidine is within the scope of "genetic engineering". Therefore, combination of the methods of Umezawa and Rangappa does not arrive at the presently claimed invention since the present claims explicitly exclude genetic engineering.

Further, Umezawa and Rangappa describe methods for differentiation of bone marrow cells and adipose tissue-derived cells into myocardial cells, respectively. They do not teach nor suggest the possibility that fat tissue-derived cells or a culture supernatant thereof may be used to induce differentiation of undifferentiated cells into a myocardial lineage. Moreover, a person of ordinary skill in the art would not expect the combination of these methods would arrive at the presently claimed invention because there is no predictability or expectation of success from combining these methods in the manner suggested by the Examiner.

The prior art can be modified or combined to reject claims as *prima facie* obvious *as long as there is a reasonable expectation of success*. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)(emphasis added). Obviousness does not require absolute predictability, however, *at least some degree of predictability is required*. *Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness*. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)(emphasis added).

Accordingly, the Examiner has failed to establish that the proposed combination of Umezawa and Rangappa yields a predictable result in order to support a *prima facie* case of obviousness. Moreover, Applicants respectfully submit that none of Egger, Bonnet, Gilmore nor Lee cure the noted deficiencies of Umezawa and Rangappa. Thus, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

In view of the foregoing, Applicants believe the pending application is in condition for allowance. A Notice of Allowance is earnestly solicited.


Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Monique T. Cole, Reg. No. 60,154 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: MAR 13 2009

Respectfully submitted,

By

*MTC*  
  
Marc S. Weiner  
Registration No.: 32,181  
BIRCH, STEWART, KOLASCH & BIRCH, LLP  
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Falls Church, Virginia 22040-0747  
(703) 205-8000  
Attorney for Applicant

Attachment: Duplicate Petition to Accept Color Drawings and/or Photographs filed on June 22, 2006

Under the Paperwork Reduction Act of 1995, no person is required to respond to a collection of information unless it displays a valid OMB control number.

<b>PETITION FEE</b> <b>Under 37 CFR 1.17(f), (g) &amp; (h)</b> <b>TRANSMITTAL</b> (Fees are subject to annual revision)  Send completed form to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	NEW
	Filing Date	June 22, 2006
	First Named Inventor	Nobuyuki TAKAKURA
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	1254-0318PUS1

Enclosed is a petition filed under 37 CFR 1.84 that requires a processing fee (37 CFR 1.17(f), (g), or (h)). Payment of \$ 130.00 is enclosed.  
 This form should be included with the above-mentioned petition and faxed or mailed to the Office using the appropriate Mail Stop (e.g., Mail Stop Petition), if applicable. For transmittal of processing fees under 37 CFR 1.17(i), see form PTO/SB/17i.

**Payment of Fees** (small entity amounts are NOT available for the petition fees).

- ☒ The Commissioner is hereby authorized to charge the following fees to Deposit Account No. 02-2448 :  
☐ petition fee under 37 CFR 1.17(f), (g) or (h) ☒ any deficiency of fees and credit of any overpayments  
 Enclose a duplicative copy of this form for fee processing.
- ☒ Check in the amount of \$ 1,070.00 is enclosed.
- ☐ Payment by credit card (Form PTO-2038 or equivalent enclosed). Do not provide credit card information on this form.

**Petition Fees under 37 CFR 1.17(f): Fee \$400 Fee Code 1462**

For petitions filed under:

- § 1.36(a) - for revocation of a power of attorney by fewer than all applicants.
- § 1.53(e) - to accord a filing date.
- § 1.57(a) - to accord a filing date.
- § 1.182 - for decision on a question not specifically provided for.
- § 1.183 - to suspend the rules.
- § 1.378(e) - for reconsideration of decision on petition refusing to accept delayed payment of maintenance fee in an expired patent.
- § 1.741(b) - to accord a filing date to an application under § 1.740 for extension of a patent term.

**Petition Fees under 37 CFR 1.17(g): Fee \$200 Fee Code 1463**

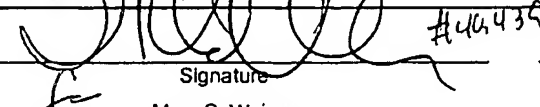
For petitions filed under:

- § 1.12 - for access to an assignment record.
- § 1.14 - for access to an application.
- § 1.47 - for filing by other than all the inventors or a person not the inventor.
- § 1.59 - for expungement of information.
- § 1.103(a) - to suspend action in an application.
- § 1.136(b) - for review of a request for extension of time when the provisions of section 1.136(a) are not available.
- § 1.295 - for review of refusal to publish a statutory invention registration.
- § 1.296 - to withdraw a request for publication of a statutory invention registration filed on or after the date the notice of intent to publish issued.
- § 1.377 - for review of decision refusing to accept and record payment of a maintenance fee filed prior to expiration of a patent.
- § 1.550(c) - for patent owner requests for extension of time in *ex parte* reexamination proceedings.
- § 1.958 - for patent owner requests for extension of time in *inter partes* reexamination proceedings.
- § 5.12 - for expedited handling of a foreign filing license.
- § 5.15 - for changing the scope of a license.
- § 5.25 - for retroactive license.

**Petition Fees under 37 CFR 1.17(h): Fee \$130 Fee Code 1464**

For petitions filed under:

- § 1.19(g) - to request documents in a form other than that provided in this part.
- § 1.84 - for accepting color drawings or photographs.
- § 1.91 - for entry of a model or exhibit.
- § 1.102(d) - to make an application special.
- § 1.138(c) - to expressly abandon an application to avoid publication.
- § 1.313 - to withdraw an application from issue.
- § 1.314 - to defer issuance of a patent.

 #44435  
 Signature \_\_\_\_\_ Date June 22, 2006  
 Marc S. Weiner \_\_\_\_\_ 32,181  
 Typed or printed name \_\_\_\_\_ Registration No., if applicable

INVENTOR'S SIGNATURE

1. INVENTOR

1. INVENTOR

Docket No.: 1254-0318PUS1  
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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In re Patent Application of:  
Nobuyuki TAKAKURA et al.

Application No.: NEW

Confirmation No.: N/A

Filed: June 22, 2006

Art Unit: N/A

For: INDUCTION OF MYOCARDIAL CELL FROM  
MAMMALIAN BONE MARROW CELL OR  
CORD BLOOD-DERIVED CELL AND FAT  
TISSUE

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Examiner: Not Yet Assigned

**PETITION UNDER 37 C.F.R § 1.84(A)(2)**  
**TO ACCEPT COLOR DRAWINGS AND/OR PHOTOGRAPHS**

MS Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Applicant hereby petitions that color drawings under 37 C.F.R. § 1.84(a)(2) be accepted in the above-identified application.

Color drawings are necessary as they are the only practical medium by which the subject matter of the present application can be disclosed. Three (3) sets of color drawings are provided, and are believed to be of sufficient quality that all details will be reproducible in black and white in the printed patent.

It is noted that black and white photocopies of any color drawing or photograph are no longer required under 37 C.F.R. § 1.84(a)(2)(iii) as of October 1, 2001.



Application No.: NEW

Docket No.: 1254-0318PUS1

**Amendment to the Specification**

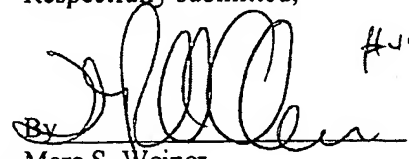
A Preliminary Amendment is being submitted concurrently herewith, providing reference to the color drawings in the first paragraph of the brief description of the drawings.

The required fee under 37 C.F.R. § 1.17(h) is attached.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: June 22, 2006

Respectfully submitted,

 #40,439  
By \_\_\_\_\_  
A Marc S. Weiner  
Registration No.: 32,181  
Attorney for Applicant

Attachment(s)

## ARTIFACT SHEET

Enter artifact number below. Artifact number is application number + artifact type code (see list below) + sequential letter (A, B, C ...). The first artifact folder for an artifact type receives the letter A, the second B, etc..  
Examples: 59123456PA, 59123456PB, 59123456ZA, 59123456ZB

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Doc Code: Computer

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Artifact Type Code: P

pages of specification.

and/or sequence listing

and/or table

Doc Code: Artifact

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Artifact Type Code: S

content unspecified or combined

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Doc Code: Artifact

Artifact Type Code: U

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Doc Code: Artifact    Artifact Type Code: C

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Microfilm(s)

Doc Code: Artifact    Artifact Type Code: F

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Video tape(s)

Doc Code: Artifact    Artifact Type Code: V

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Model(s)

Doc Code: Artifact    Artifact Type Code: M

☐

Bound Document(s)

Doc Code: Artifact    Artifact Type Code: B

☐

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marked Proprietary, Trade Secrets, Subject to Protective Order,  
Material Submitted under MPEP 724.02, etc.

Doc Code: Artifact    Artifact Type Code X

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Other, description: \_\_\_\_\_

Doc Code: Artifact    Artifact Type Code: Z

March 8, 2004

Docket No.: 1254-0318PUS1  
(PATENT)

RECEIVED  
28 JUL 2006  
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International Division

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:  
Nobuyuki TAKAKURA et al.

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Confirmation No.: N/A

Filed: June 22, 2006

Art Unit: N/A

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TISSUE

Examiner: Not Yet Assigned

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Birch, Stewart, Kolasch & Birch, LLP

MSW/smt

BEST AVAILABLE COPY

<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371</b>		<b>ATTORNEY'S DOCKET NUMBER</b> 1254-0318PUS1
<b>INTERNATIONAL APPLICATION NO.</b> PCT/JP2004/019665	<b>INTERNATIONAL FILING DATE</b> 21 December 2004	<b>U.S. APPLICATION NO. (Form No. 2, CFR 1.5)</b> <b>10/584028</b>
<b>TITLE OF INVENTION</b> INDUCTION OF MYOCARDIAL CELL FROM MAMMALIAN BONE MARROW CELL OR CORD BLOOD-DERIVED CELL AND FAT TISSUE		<b>PRIORITY DATE CLAIMED</b> 25 December 2003
<b>APPLICANT(S) FOR DO/EO/US</b> Nobuyuki TAKAKURA and Yoshihiro YAMADA		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<p>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a submission under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a submission under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</p> <p>4. <input type="checkbox"/> The US has been elected (Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371 (c)(2)).</p> <p>a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</p> <p>b. <input checked="" type="checkbox"/> has been communicated by the International Bureau.</p> <p>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</p> <p>6. <input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <p>a. <input checked="" type="checkbox"/> is attached hereto.</p> <p>b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).</p> <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</p> <p>b. <input type="checkbox"/> have been communicated by the International Bureau.</p> <p>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</p> <p>d. <input checked="" type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p> <p>Items 11 to 20 below concern document(s) or information included:</p> <p>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input checked="" type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A preliminary amendment.</p> <p>14. <input type="checkbox"/> An Application Data Sheet under 37 CFR 1.76.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A power of attorney and/or change of address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 37 CFR 1.821 - 1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published International Application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p>		